35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has maintained rejection of claims 1, 5-7, 12-14, 18-20, 25 and 26 under U.S.C. 112, second paragraph as being indefinite for failing to point out and distinctly claim the invention. The Examiner's rejections are respectfully traversed. Claims 1, 7, 12-14, 20, 25 and 26 have now been amended.

The Examiner states that the term "modified LDL" is an unclear term, having no art recognized meaning and the meaning of the term not disclosed in the specification, thus rendering claim 1 indefinite. The Examiner further states that the references disclosed were not of record, and were not considered.

Applicant wishes to point out that one skilled in the art would readily recognize the meaning of the phrase "modified LDL" since, as is evident from numerous prior art publications, (see, for example, U.S. Pat. No. 5,409,710 to Leonard; Pech MA, et al. Ann Biol Clin (Paris) 1992;50:213-27; Mol MJ at al. Neth J Med 1993;43:83-90; and Hoff HF and Hoppe G Curr Opin Lipidol 1995;6:317-25, copies of which are enclosed herewith), this phrase is an accepted art term having a well defined meaning. Thus, it is the applicant's strong opinion that the term "modified LDL" recited in claims 1, 5, 14 and 18 is a well-defined art term having an art-recognized meaning, and as such, claims 1, 5, 14 and 18, and claims directly or indirectly dependent therefrom are not rendered indefinite by the use of this phrase.

With respect to claims 7 and 20 the Examiner states that the phrase "active derivative", lacks antecedent basis thus rendering these claims indefinite. With respect to claims 7 and 20 the applicant wishes to point out that the limitation recited in these claims: "...wherein said active component is an active derivative of oxidized low density lipoprotein (Ox LDL)." derives antecedent basis directly from the recitation of "an active component" in claims 1 and 14, respectively: "An immunological oral tolerance-inducing composition... comprising an active component selected from...".

To further define the claims of the present invention, and to expedite prosecution of this case, claims 7 and 20 are hereby amended to include the limitation: "...wherein said active component is a functional derivative of oxidized LDL.", which derives antecedent basis from the recitation, in claims 1 and 14, of "...the group consisting of modified low density lipoprotein, oxidized low density lipoprotein (Ox LDL), heat shock protein 60/65 (HSP 60/65), beta$_2$-glycoprotein-1 (β_2-GP-1), **functional derivatives thereof**..." (emphasis added), thus overcoming the Examiner's rejections.

With respect to claims 12 and 25 the applicant wishes to point out that the limitation recited in claims 12 and 25: "...wherein said active component is lysophosphatidyl choline (LPC)," derives antecedent basis directly from the recitation of "an active component selected from the group consisting of modified low density lipoprotein, oxidized low density lipoprotein (Ox LDL), heat shock protein 60/65 (HSP 60/65), beta$_2$-glycoprotein-1 (β_2-GP-1), functional derivatives thereof...," in claims 1 and 14, respectively. As the Examiner has pointed out (paragraph 9 of Official Action): "LPC is a derivative of LDL. LPC is also a derivative of Ox LDL. LPC is a modified LDL."

To further define the claims of the present invention, and to expedite prosecution of this case, claims 12 and 25 are hereby amended to include the limitation: "...wherein said modified low density lipoprotein is lysophosphatidyl choline (LPC).", which derives antecedent basis from the recitation, in claims 1 and 14, of "...the group consisting of modified low density lipoprotein, oxidized low density lipoprotein (Ox LDL), heat shock protein 60/65 (HSP 60/65), beta$_2$-glycoprotein-1 (β_2-GP-1), functional derivatives thereof..." (emphasis added), thus overcoming the Examiner's rejections.

With respect to claims 13 and 26, the Examiner has pointed out that the recitation "wherein said LDL..." lacks antecedent basis in independent claims

1 and 14, respectively. Applicant wishes to point out that claims 1 and 14 recite : "oxidized low density lipoprotein (OxLDL)...", providing antecedent basis for the recitation of MDA-LDL in dependent claims 13 and 26.

To further define the claims of the present invention, and to expedite prosecution of this case, claims 13 and 26 are hereby amended to include the limitation: "...wherein said modified low density lipoprotein is malondialdehyde LDL (MDA-LDL).", which derives antecedent basis from the recitation, in claims 1 and 14, of "...the group consisting of modified low density lipoprotein, oxidized low density lipoprotein (Ox LDL), heat shock protein 60/65 (HSP 60/65), beta$_2$-glycoprotein-1 (β_2-GP-1), functional derivatives thereof..." (emphasis added), thus overcoming the Examiner's rejections.

In view of the above amendments and remarks, Applicant believes to have overcome the 35 U.S.C. § 112, second paragraph, rejections.

35 U.S.C. § 112, First Paragraph, Rejections

The Examiner has maintained the rejection of claims 1, 5-7, 12-14, 18-20, 25 and 26 under U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey that the inventors had possession of the claimed invention. The Examiner's rejections are respectfully traversed. Claims 1, 7, 12-14, 20, 25 and 26 have now been amended.

With regard to amended claim 1, the amended limitation: "the composition being formulated for inducing oral tolerance" has been cancelled, rendering Examiner's rejection moot.

To further define the claims of the present invention, and to expedite prosecution of this case, claims 1 and 14 has now been amended to include the limitation: "...a therapeutically effective amount of an active component...", thus restricting the instant invention to doses or amounts suitable for treatment of atherosclerosis. Support for such amendments can be found throughout the

instant Specification, for example, on page 18, lines 27-29, and on page 19, lines 17-21.

With regard to amended claim 14, the Examiner further states that there is no support in the specification as originally filed for the recitation "thereby inhibiting at least one atherosclerosis-related symptom in said subject".

Applicant wishes to point out that the instant specification, as originally filed, discloses methods and compositions for the prevention and/or treatment of atherosclerosis by immunological oral tolerance, and as such discloses, in substantial detail, methods and criteria for determining "...at least one atherosclerosis-related symptom..." in a subject following treatment according to the instant invention. For example, in the description of oral tolerance to Ox LDL on page 13, lines 15-19, the "stimulation and production of cytokine TGFβ and the development of non-specific suppressor T-cells" is disclosed. Methods of determining atheroslerosis related parameters are described in even greater detail throughout the Materials and Methods, and Examples sections of the instant specification: determination of the anti-Ox LDL antibody titers (Page 16, lines 10-25), detection of anti-phospholipid antibodies (page 17, lines 12-24); determination of cytokine profile and level (page 18, lines 10-15), serum evaluation for anti-Ox LDL, anti-PL, serum lipid profile and immunohistochemistry using monoclonal anti-CD3, CD4, CD8, anti-macrophage, smooth muscle cell, and lymphocyte activation markers (page 19, lines 15-30) of hearts from Ox LDL-treated mice (Example 2); and evaluation of atherosclerotic lesions in hearts, serum cholesterol and antibody levels in mice following oral feeding of Ox LDL (Example 1, page 18). An additional measure of atherosclerosis-related symptoms is provided in "Adoptive transfer experiments" (page 22), describing the evaluation of effect of oral feeding of Ox LDL on passive transfer of immunity by sensitized T-cells. The abovementioned assays of "atherosclerosis-related symptoms" are art recognized assays available to one of ordinary skill in the art. In view of the objective evidence of support throughout the instant specification

provided hereinabove, Applicant is of the strong opinion that the limitations recited in amended claim 14 do not constitute new matter, and as such, amended claim 14 is allowable.

In view of the above amendments and remarks, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph, rejections.

35 U.S.C. § 102(b) Rejections - Yesair

The Examiner has rejected claims 1, 5, 7, 12, 14, 18, 20 and 25 under 35 USC § 102(b) as being anticipated by Yesair (U.S. Pat. No. 4,874,769). The Examiner's rejections are respectfully traversed. Claims 1 and 14 have now been amended.

The Examiner states that Yesair anticipates the pharmaceutical compositions and methods of the present invention since Yesair teaches a composition for oral administration containing LPC and other lipids, that LPC is a derivative of Ox LDL and a modified LDL, that Yesair teaches in vivo administration of said composition to the same population as taught by the present invention, and that it is an inherent property that administration of the claimed composition results in the method of claim 14, because the method as taught by Yesair et al. involves administration to any individual. The Examiner further states that the references disclosed were not of record, and were not considered.

The present invention relates to a composition for inducing oral tolerance and to methods using such a composition for preventing or treating atherosclerosis. As demonstrated in the Examples section of the instant application, the present inventors have demonstrated, for the first time, a substantial reduction in atherosclerosis in LDL-RD mice using the compositions of the present invention (see page 18, Example 1).

Applicant would like to re-emphasize, that the compositions taught by Yesair would not be useful in reducing atherosclerosis in a subject, since these compositions are simply not formulated for the purpose of inducing immune

tolerance to LPC.

Yesair teaches the inclusion of 1.0- 30 % LPC in lipid micelles, in order to enhance the intestinal absorption of the fatty acids of the micelles into the lymphatic system (see column 7, lines 5-50).

Since presentation of the tolerizing antigen at the gut associated lymphoid tissue depends on the exposure of relevant epitopes, it is highly unlikely that micelle formulations, which surround the active components with lipid vehicle components, would constitute an immunological oral tolerance-inducing composition. Indeed, micelles are generally not included in the methods of administration cited for induction of oral tolerance, but rather for enhanced systemic uptake of drugs and fat-soluble substances (see Shen H et al., Adv Drug Deliv Rev 2001; 50 Suppl 1: 5103-25, and Maurer N et al., Expert Opin Biol Ther 2001; 1: 923-47, copies of which are enclosed herewith).

Thus, it is applicant's strong opinion that Yesair et al. does not teach or infer the claimed compositions and methods for treating and/or preventing atherosclerosis of the present invention, therefore claims 1 and 14, and claims dependent therefrom, are neither anticipated nor are they rendered obvious by the teachings of Yesair.

To further distinguish the present invention from Yesair, et al., and to expedite the prosecution of this case, claims 1 and 14 has now been amended to include the limitation: "...a therapeutically effective amount of an active component...", thus restricting the instant invention to doses or amounts suitable for treatment of atherosclerosis. Support for such amendments can be found throughout the instant Specification, for example, on page 18, lines 27-29, and on page 19, lines 17-21.

35 U.S.C. § 102(e) Rejections - Witztum et al.

The Examiner has rejected claims 1, 5- 7, 12 and 13 under 35 USC § 102(e) as being anticipated by Witztum et al. (U.S. Pat. No. 6,225,070). The

Examiner's rejections are respectfully traversed. Claims 1, 12 and 13 have now been amended.

The Examiner states that Witztum teaches a composition containing MDA-LPL or Acetyl-LDL in PBS which anticipate the compositions of the present invention. The Examiner further states that the references disclosed were not of record, and were not considered.

Contrary to the Examiner's assertion, Witztum et al. do not describe compositions or the use thereof for treatment and/or prevention of atherosclerosis. Witztum et al. teach various methods for preparation of "...Artifactual Oxidation Protected Oxidized Lipoprotein Antigens" and their use as antigens for "...screening of plasma, hybridoma supernatants, ascites and purified antibodies...". The explicitly stated intent of the invention of Witztum et al. is to "...provide monoclonal antibodies for in vivo and in vitro use..."(column 3, line 59-60).

Since compositions commonly used for immunological screening are substantially different from those used in the treatment and/or prevention of disease, the immunological screening being performed in-vitro, formulated to conform to the biochemical parameters of the cell-culture environment, and the antigenicity of "self" molecules cannot be easily deduced. The Examiner's attention is respectfully directed to the Ogra et al. and Chen et al. references (Ogra et al. Clin Microbiol Rev 2001; 14: 430-45 and Chen et al. J Control Release 2000; 67:117-28), copies of which are enclosed herewith. Thus, it is Applicant's strong opinion that one of ordinary skill in the art would not be motivated to prepare or orally administer the antigens described by Witztum et al. in order to induce immune tolerance in an animal or human subject, and that preparing or orally administering such antigens in order to induce immune tolerance would require that one of ordinary skill in the art engage in undue experimentation. Thus, the teachings of Witztum et al. cannot be interpreted as anticipating or rendering obvious the compositions or methods claimed in claims 1, 5- 7, 12 and 13 of the present invention.

To further distinguish the present invention from Witztum et al. and to expedite prosecution of this case, claims 1 and 14 have now been amended to include the limitation: "...a therapeutically effective amount of an active component...", thus restricting the instant invention to doses or amounts suitable for treatment of atherosclerosis. Support for such amendments can be found throughout the instant Specification, for example, on page 18, lines 27-29, and on page 19, lines 17-21.

35 U.S.C. § 103(a) Rejections

Strober et al. in view of Hansson et al., Resch et al. and Sima et al.

The Examiner has rejected claims 1, 5- 7, 12, 14, 18-20 and 25 under 35 USC § 103(a) as being unpatentable over Strober et al. in view of Hansson et al., Resch et al. and Sima et al. The Examiner's rejections are respectfully traversed. Claims 1, 12, 14 and 25 have now been amended.

The Examiner states that Strober et al. teach compositions of autoimmune antigens and the use of said compositions to treat autoimmune disease and that this method can be used to treat autoimmune disease mediated by T cells and B cells. The Examiner further states that Hansson et al. and Sima et al. teach that Ox-LDL functions as an autoantigen in atherosclerosis and that Resch et al. teaches that autoantibodies bind modified/derivatives of LDL, and therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have created the claimed invention. The Examiner further states that the references disclosed were not of record, and were not considered.

Applicant wishes to point out that Strober et al. do not describe nor do they suggest compositions suitable for treating atherosclerosis, let alone describe or suggest methodology for treating and/or preventing atherosclerosis.

Strober et al. teach the use of a method for enhancement of oral tolerance to autoimmune diseases, many of which are specified in the claims and detailed description, and "any other autoimmune disease now known or

discovered in the future". Nowhere is atherosclerosis in this recitation of autoimmune diseases, since atherosclerosis, and its related conditions, is not recognized in the art as an autoimmune disease.

Applicant has discussed, in detail, the controversial nature of atherosclerosis' inclusion in the category of autoimmune diseases. For further details, the Examiner is hereby directed to the Emeson et al. and Meir references (Emeson et al. Am J Pathol 1993;142: 1906-15 and Meir, et al. Commentaries, Int. Atheroscler Soc.), copies of which are enclosed herewith. These distinctive features of atherosclerosis would prevent an ordinary skilled artisan from applying the teachings of Strober et al. to treating atherosclerosis since atherosclerosis would not be recognized by one of ordinary skill in the art as an autoimmune disease.

The Examiner states that Hansson et al., Resch et al. and Sima et al. all teach that Ox LDL functions as an autoantigen in atherosclerosis, and the importance of inflammation and immune response in the pathogenesis of atherosclerosis, and that it would have been *prima facie* obvious to one of ordinary skill in the art to have created the claimed invention using the teachings of Strober et al. in view of the teachings of Hansson et al., Resch et al. and Sima et al.

Contrary to Examiner's conclusion, Applicant is of the strong opinion that the role of the immune response in the pathogenesis and treatment of atherosclerosis remains controversial (see, for example, Meir at al., as discussed above and enclosed herewith), and one ordinarily skilled in the art would not be motivated to use modified LDL and other antigens recited in the claimed invention for treatment and/or prevention of atherosclerosis especially via oral induction of immune tolerance.

The Examiner is hereby respectrfully directed to the references enclosed herewith describing the induction of autoimmune disease in animal models following immunization with classic autoantigens, such as collagen in RA (reviewed by Williams RO Clin Exp Immunol 1998; 114:330) and myelin

basic protein in rat model of multiple sclerosis (Fujinam et al. J Exp Med 1978;148:1716). In contrast, immunization with oxidized LDL causes a reduction in the severity of atherosclerosis (Palinski et al. PNAS 1995;92:821-25; George et al. Atherosclerosis 1998;138:147-52; Freigang et al. Arterioscler Thromb Vasc Biol 1998;18:1972-82 and Zhou et al. Arterioscler Thromb Vasc Biol 2001;21:108-114, copies of which are enclosed herewith). A Table (Table I) summarizing the abovementioned differences between the immunological response to classic autoantigens and that of Ox LDL is enclosed herewith.

While techniques of inducing oral tolerance are well known in the art for many years, the parameters useful for inducing effective oral tolerance cannot be deduced from antigenic activity in conventional immunization, and must result from extensive and undue empirical experimentation. Thus, one ordinarily skilled in the art would not have expected to prepare such compositions or develop the methods of the present invention with a reasonable degree of success without having to resort to undue trial and error experimentation.

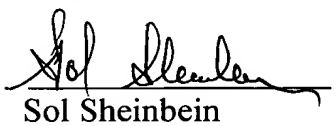
Indeed, many studies have demonstrated the complexities inherent in manipulating the "balance between reacting and non-reacting" in the immune system (for recent reviews of problems in oral and mucosal tolerance, see Ogra et al. Clin Microbiol Rev 2001;14:430-45; Chen et al. J Control Release 2000;67:117-28; and Lehner et al. J Infect Dis 1999; 179 Suppl 3:S489-92, copies of which are enclosed herewith). Indeed, it is well known in the art that oral feeding of even well-defined autoantigens, such as ovalbumin, can unexpectedly, and unpredictably, induce autoimmune disease (Blanas, E et al., Science 1996, 274;1707, enclosed herewith). Furthermore, oral feeding is a particularly unpredictable route of administration, due to digestive and metabolic influences on the antigens. Thus, the existence of anti-oxidized LDL antibodies in atherosclerosis does not make *prima facie* obvious the usefulness of oxidized LDL for inducing oral tolerance.

Since the immune response to oxidized LDL is not that which would be expected for a classic autoimmune antigen, and since the prior art cited herein fails to teach or even suggest treatment of atherosclerosis via oral induction of immune tolerance, it is Applicant's strong opinion that the immunological oral tolerance inducing compositions and methods for their use in treating and preventing atherosclerosis of the present invention are patentable over Strober in view of Hansson et al., Resch et al. and Sima et al.

Further, and in addition to the abovementioned, Applicant wishes to point out that among the criteria employed to determine novelty and non-obviousness is the demonstration of new and unexpected results. While reducing the present invention to practice, employing the methodology taught in the instant application, Applicant has uncovered, for the first time, that oral feeding of the recited therapeutic amounts of human Ox LDL to genetically susceptible LDL-RD mice reduces the incidence of atherosclerotic aortic sinus lesions in a dose dependent manner, downregulates the lymphocyte proliferative response, induces the important immune-suppressive cytokine IL-10 and inhibits the pro-inflammatory cytokine IFN-γ (see accompanying Declaration). It is Applicant's strong opinion that this demonstration, of the importance of accurate dosage, and the ability to evaluate immune suppressive response via cytokine levels, as taught in the instant specification, further distinguish the present invention from the abovementioned prior art.

In view of the above amendments and remarks it is respectfully submitted that claims 1, 5-7, 12-14, 18-20, 25 and 26 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,



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Date: November 21, 2002.

Enc.
Version with marking to show changes made
A three month extension fee
Copies of references to be made of record
Table I
Declaration

VERSION WITH MARKING TO SHOW CHANGES MADE

In the Specification:

Please amend page 1, line 1 by adding the following cross-references information:

This application is a National Phase of PCT/IL99/00519, filed September 30, 1999, which claims priority from Israel Patent Application No. 126447, filed October 4, 1998.

In the Claims:

1. (Twice Amended) An immunological oral tolerance-inducing composition for prevention and/or treatment of atherosclerosis, comprising a therapeutically effective amount of an active component selected from the group consisting of modified low density lipoprotein, oxidized low density lipoprotein (Ox LDL), heat shock protein 60/65 (HSP 60/65), $beta_2$-glycoprotein-1 ($beta_2$GP-1), functional derivatives thereof and mixtures thereof, in combination with a pharmaceutically acceptable carrier for oral administration.~~, the composition being formulated for inducing oral tolerance.~~

7. (Amended) An immunological tolerance-inducing composition according to claim 1, wherein said active component is ~~an active~~ functional derivative of oxidized low-density lipoprotein (Ox LDL).

12. (Twice Amended) An immunological tolerance-inducing composition according to claim 1, wherein said ~~active component~~ modified low density lipoprotein is lysophosphatidyl choline (LPC).

13. (Amended) An immunological tolerance-inducing composition according to claim 1, wherein said modified low density lipoprotein~~LDL~~ is malondialdehyde LDL (MDA-LDL).

14. (Twice Amended) A method for prevention and/or treatment of atherosclerosis in a subject, comprising administering a therapeutically effective amount of an immunological oral tolerance-inducing composition comprising an active component selected from the group consisting of modified low density lipoprotein, oxidized low density lipoprotein (Ox LDL), heat shock protein 60/65 (HSP 60/65), $beta_2$-glycoprotein-1 ($beta_2$GP-1), functional derivatives thereof and mixtures thereof, in combination with a pharmaceutically acceptable carrier for oral administration, thereby inhibiting at least one atherosclerosis-related symptom in said subject.

20. (Amended) A method according to claim 14, wherein said active component is ~~an active~~ functional derivative of oxidized low-density lipoprotein (Ox LDL).

25. (Twice Amended) A method according to claim 14, wherein said ~~active component~~ modified low density lipoprotein is lysophosphatidyl choline (LPC).

26. (Amended) A method according to claim 14, wherein said ~~LDL~~ modified low density lipoprotein is malondialdehyde LDL (MDA-LDL).